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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
1637	
MAIL DATE	**DELIVERY MODE**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,101	TERAMAE ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-26* is/are pending in the application.

4a) Of the above claim(s) *21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application has been transferred from Surchira Panda of Art Unit 1637 to Cynthia Wilder of Art Unit 1637. Any future correspondence should be directed to Cynthia Wilder whose contact information appears at the end of this Office action.

2. Applicant's amendment filed August 12, 2004 is acknowledged and has been entered. Claim 14 has been amended. Claims 1-11 has been cancelled. Claims 12-26 are pending. Claims 21-26 are withdrawn from consideration as being drawn a non-elected invention. Claim 12-20 are discussed. All of the arguments have been thoroughly reviewed and considered but are deemed moot in view of the new grounds of rejections present in this Office action. This Office action is made Non-Final as the new ground(s) of rejections were not necessitated by Applicant's amendment of the claims. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Objections and Rejections

4. The objection to the specification concerning the sequence requirement is withdrawn in view of Applicant's submission of a substitute sequence listing. The prior art rejections under 35 USC 102(b) as being anticipated by Yoshimoto et al is withdrawn in view of Applicant's amendment.. The prior art rejections under 35

USC 103(a) as being unpatentable over Yoshimoto et al in view of Nakatani et al is withdrawn in view of Applicant's amendment.

New Ground(s) of Rejections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 12-20 are indefinite in confusing at the recitation "two partial sequences thereof" as recited in the context of step (i) of claim 12 because it cannot be determined what is meant by partial sequence in the context of the claims. It is unclear what encompasses the "partial sequences" of the single stranded target nucleic acid. For example, it cannot be determined if Applicant is suggesting that the single stranded target nucleic acid is cleaved at certain points along the single strand of the target nucleic acid or modified in some manner to produce the 'partial sequences' or if Applicant is suggesting something entirely different. The specification does not provide a limiting definition for the terms and thus a clear interpretation of Applicant's intent cannot be ascertained. Clarification is required.

Claim Interpretation

The claims are ambiguous for the reasons discussed above. The specification does not provide a limiting definition as to what is encompassed by

the limitation two partial sequences of a target nucleic acid. Accordingly the limitation is being interpreted as any sequence before and after a mutated base or SNP of a target nucleic acid sequence.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 12, 13, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bao et al (20030129611, July 2003) in view of Yoshimoto et al. (Chemical Communication, Issue 24, pages 2960-2961, October 2003). Regarding claim 12, Bao et al teach a method for detecting a gene mutation comprising: forming a double stranded nucleic acid from a single stranded

nucleic acid having a target based composed of one or more continuous bases and two partial sequences thereof with the target base there between, and two single stranded detecting nucleic acids complementary to the two partial sequences with the target base there between and identifying the gene mutation using fluorescent detection that uses resonance energy transfer (see Figures 1 and 2; wherein SEQ ID NOS: 11 and SEQ ID NO: 12 represent the two single stranded nucleic acid complementary to the two partial sequences with the target base and SEQ ID NO: 10 representing the target sequence having a mutation between SEQ ID NOS: 11 and 12). Bao et al differs from the instant invention in that the reference does not teach wherein a hydrogen bond is formed by the target base and a receptor by inserting a receptor having hydrogen bonding characteristics into the double stranded nucleic acid and then identifying the gene mutation where the receptor bonds to the target base.

Yoshimoto et al provides a method for fluorescence detecting of a mutation in a target nucleic acid by hydrogen bond forming small compounds. Yoshimoto et al recognizes that while such method as high density arrays, primer extension methods, real-time PCR, and Invader assays (which includes various forms of fluorescent detections), all are used for detecting a mutation in a target nucleic acid, these methods require several time consuming steps, use of several kinds of fluorophore-labeled oligonucleotides (ODNs) and/or special enzymes. (see first paragraph of page 2960 at col. 1). Yoshimoto further recognizes that while mass spectroscopy has recently been applied to genotyping, it's use is at a disadvantage because careful treatment are required to ensure purity of the

sample. Yoshimoto attempt to solve the problems of those techniques noted above and taught by Bao et al by providing a quick, simple and cost effective method for the routine detecting of mutations (see col. 1 of page 2960 for discussion).

Yoshimoto teach a method similar to that of Boa et al for detecting a gene mutation comprising forming a double strand nucleic acid from a single stranded nucleic acid having a target base composed of one or more continuous bases and two partial sequences there with the target base there between; and a probe comprising two separate regions, wherein each region is complementary to each of partial sequences with the target base there between and identifying the gene mutation, wherein said identifying step comprising forming a hydrogen bond by the target base and a receptor by inserting a receptor having hydrogen bonding characteristics into the double stranded nucleic acid (see Figure 1 and col. 1-2 of page 2960). Yoshimoto et al teach that they expect that the use of low molecular weight ligands as recited in their method offers a novel approach to a simple, low cost assay for SNP (mutation) typing (see page 2961, col. 2, lines 10-14).

It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to modify the method of Bao et al to encompass the use of a receptor having hydrogen bonding characteristics to to detect the gene mutation in the target nucleic acid rather than the donor and acceptor molecular beacons which result in FRET as taught by Bao et al to alleviate some of the disadvantage of the FRET system and improve gene

mutation detection. The ordinary artisan would have been motivated to use the receptor having hydrogen bonding characteristics based on the advantages taught by Bao et al that such method provides a more simple, quick and cost-effective approach to mutation typing. Likewise, it would have been *prima facie* obvious to the ordinary artisan at the time of the claimed invention that one could substitute one known option for another in assays for mutation typing, namely the use of receptor having hydrogen bonding characteristic rather than dual molecular beacons using FRET as taught by Bao et al or any of the other assays recited above, since all of these techniques are within the ordinary artisan's technical grasp and further since the use of a receptor having hydrogen bonding characteristics, such as those recited in the claims, do not negatively alter, affect or modify fluorescent detection of the target mutation. Thus, one of ordinary skill in the art at the time of the claimed invention could expect a reasonable expectation of success and attempt to improve detection of the target mutation based on the combined teachings of Bao et al in view of Yoshimoto et al.

Regarding claim 13, Yoshimoto et al. teach wherein the receptor has a heterocyclic aromatic group and is stabilized by the formation of a hydrogen bond to the target base and a stacking interaction with the base adjacent to the receptor to form a pair with the target base (see Table 1 on page 8982 where structure of AMND = receptor of instant claim is shown. The structure of AMND shown has a heterocyclic aromatic group. See page 8982 col. 2 par. 1 where determination of stability between AMND and C indicates the significant role of stacking of AMND with nucleobases flanking the AP site is taught. Also see last

line of this par. where conclusion is stated. "Therefore, AMND should bind to C in cooperative fashion, that is, hydrogen bonding with C and stacking with nucleobases flanking the AP site". Thus Yoshimoto et al. teach wherein the receptor has a heterocyclic aromatic group and is stabilized by the formation of a hydrogen bond to the target base and a stacking interaction with the base adjacent to the receptor to form a pair with the target base).

Regarding claim 14, Yoshimoto et al. teach wherein the receptor is at least one of a naphthylidine derivative, a quinoline derivative, a pteridine derivative, a coumarin derivative, an indazol derivative, an alloxazine derivative and amyloride (see page 8982 par. 2 where AMND taught is a methyl napthyridine hence teaching wherein the receptor is a naphthylidine derivative).

Regarding claim 18, Yoshimoto et al. teach wherein the receptor shows fluorescence emitting characteristics and the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted (see fig. 4 where the receptor shows fluorescence emitting characteristics and the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted).

10. Claims 15-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bao et al in view of Yoshimoto et al. as applied to claim 1-14 and 18 above, and further in view of Nakatani et al. (2001) J. Am. Chem. Soc. 123: 12650-12657 (provided by Applicant in IDS).

Regarding claim 15, Boa et al in view of Yoshimoto et al. teach detection of a gene mutation as described above.

Bao et al and Yoshimoto et al. do not expressly teach wherein the receptor is fixed to a substrate. However the use of solid supports in methods of detecting mutation by the techniques mention previously are well known in the prior art.

For example, Nakatani et al. teach wherein the receptor is fixed to a substrate (see page 12651 col. 2 par. 2 where naphtyridine derivative referred as compound 2 is immobilized onto dextran coated gold surface to develop a mismatch detecting sensor useful for a surface Plasmon resonance (SPR) assay.

Regarding claim 16, Nakatani et al. teach wherein the gene mutation is identified on the basis of the change of a signal strength of a surface plasmon resonance due to the bond of the target base and the receptor (see page 12651 col. 2 par. 2 where a mismatch detecting sensor useful for a surface plasmon resonance (SPR) assay is described. They go on to teach differentiation of 652 bp of PCR products of a G/C heterozygote from those of a G/G homozygote of HSP70-2 gene regarding the base at a nucleotide number 2345. Thus teaching Nakatani et al. teach wherein the gene mutation is identified on the basis of the change in signal strength of a surface plasmon resonance due to the bond of the target base and the receptor).

Regarding claim 17, Nakatani et al. teach development of sensor where a component of the reaction mix namely receptor is fixed on substrate to develop sensor that is suitable for surface plasmon resonance (SPR) assay.

In the instant claims (15 and 17) applicant recites fixing a different component of the assay namely one detecting nucleic acid to a substrate instead of the fixing the receptor as taught by Nakatani et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Nakatani et al. in the method of Bao et al and Yoshimoto et al. to fix any of the components either the receptor or the one detecting nucleic acid to a substrate to form the sensor and then add the remaining components required to form the double stranded hybrid (claims 15 and 17). Thus, Nakatani et al. teach wherein one detecting nucleic acid is fixed to a substrate and the double-stranded nucleic acid is formed by dropping on the substrate the single-stranded target nucleic acid, the other detecting nucleic acid and the receptor.

See 2144.04 Legal Precedent as Source of Supporting Rationale [R-6] - 2100 Patentability IV. CHANGES IN SIZE, SHAPE, OR SEQUENCE OF ADDING INGREDIENTS C. Changes in Sequence of Adding Ingredients. See *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.).

Regarding claims 19 and 20, Yoshimoto et al. teach wherein the receptor shows fluorescence emitting characteristics and the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted (see Fig. 4 where the receptor shows fluorescence

emitting characteristics and the gene mutation is identified as a change of fluorescence strength of the double-stranded nucleic acid into which the receptor is inserted).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Nakatani et al. in the method of Bao et al in view of Yoshimoto et al. The motivation to do so is provided to one of ordinary skill in the art by the teachings of Nakatani et al that "We have developed a mismatch-detecting sensor useful for a surface Plasmon resonance (SPR) assay by immobilizing 2 (note added by Examiner 2 = naphthyridine compound) onto the dextran-coated gold surface." (see page 12651 col. 2 par. 2). They go on to teach its successful use in determining gene mutation. Hence, one of ordinary skill in the art at the time of the claimed invention would have a reasonable expectation of success in being able to develop a sensor for detecting mutations using the receptor taught by Yoshimoto et al. in the method of Boa et al and immobilizing the components to a surface as taught by Nakatani et al for the obvious benefit of caring out additional and more sensitive and specific means of detecting the mutation, said means being surface plasmon resonance.

Conclusion

11. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Examiner, Art Unit 1637